DIABETES MELLITUS AND ARTERIOGRAPHICALLY-DOCUMENTED CORONARY ARTERY DISEASE

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Abstract:
Diabetics are at increased risk for coronary heart disease even after accounting for other risk factors, and the impact of diabetes mellitus may be particularly strong among females and at adverse levels of other risk factors. Therefore, the independent relation of diabetes to arteriographically-documented coronary artery disease (CAD) was examined in 5620 patients (18% female) referred to two Milwaukee hospitals from 1972 to 1986. As assessed by questionnaire, the prevalence of diabetes mellitus among these patients was 8% *(n* = 466). Diabetics had increased CAD (assessed by the number and severity of stenoses) even after accounting for levels of total and high-density lipoprotein cholesterol, triglycerides, hypertension, obesity, smoking, and alcohol consumption. In addition, regression analyses indicated that as compared with nondiabetics, female diabetics tended to have a greater increase in CAD than did male diabetics *(p = 0.06* for sex x diabetes interaction), Although adverse levels of other risk factors did not increase the association between diabetes and CAD, female diabetics who were using oral hypoglycemics or insulin showed almost a two-fold increase in CAD severity *(p* <0.01). Results suggest that the higher relative risk of coronary heart disease among female (vs male) diabetics may be due to a proportionately greater increase in atherosclerosis.
Keywords: Diabetes, Coronary artery disease, Arteriography

Article:

INTRODUCTION

Autopsy [1, 2], clinical [3, 4], and prospective epidemiologic studies [5-11] indicate that diabetes mellitus confers at least a twofold increased risk for coronary heart disease (CHD) mortality. Although the principal cause of this arterial disease among both insulin-dependent (type 1) and noninsulin-dependent (type 2) diabetes is atherosclerosis, the risk of congestive heart failure is also increased [12]. Furthermore, with few exceptions [10], diabetes is more strongly related to CHD among premenopausal females than in similarly aged males.

Ecologic and migrant studies suggest that the increased CHD mortality among diabetics in industrialized countries may be due to an increased prevalence of hyperlipidemia, obesity, and hypertension [13]. Although diabetics show an increased clustering of risk factors [14], this aggregation accounts for only a small proportion of their excess CHD, and diabetes has remained an independent predictor of clinical disease in all prospective studies [5-11]. In addition, diabetics who are young [15], who smoke cigarettes [16], are hypertensive [15], obese [17], hyperlipidemic [18], or who have decreased levels of high-density lipoprotein (HDL) cholesterol [6] may be at very high risk for CHD.

Many of the clinical and prospective studies of diabetics have been limited by small numbers of deaths, and all have relied on clinical diagnoses of CHD, without knowledge of the underlying anatomic substrate. Although differences in coronary atherosclerosis between diabetics and nondiabetics have been examined in arteriography studies [18-24], possible effects of other risk factors have not always been considered. However, Abadie *et al.* [24] found that diabetics did not have increased CAD as compared with controls matched for age, sex, blood pressure, total cholesterol, and triglycerides. Another report [18] suggested that the increased CAD among diabetics was particularly evident at elevated triglyceride levels, In contrast, in a previous analysis of 2006

patients [21], we found that diabetics had more severe CAD independently of lipid levels, smoking, hypertension, obesity, and alcohol intake; HDL cholesterol levels, however, were not included in these analyses.

The objective of the current study of over 5000 patients is to examine sex differences in the relation of diabetes to CAD, and possible interactions of diabetes with age, obesity, hypertension, cigarette smoking, and levels of plasma lipids and HDL cholesterol. In addition, the relative importance of other risk factors in diabetics and nondiabetics is compared. Possible referral biases inherent in hospital-based studies of diabetics are discussed.

METHODS

Population and disease status

The Milwaukee Cardiovascular Data Registry is a clinical database consisting of patients referred to selected Milwaukee hospitals (St Luke's and Zablocki Veterans Administration Medical Center) for diagnostic coronary angiography. The current study is restricted to whites who were examined from 1972 to 1986, and for whom plasma levels of both total cholesterol and triglycerides were measured. (Only 27 black diabetics underwent arteriography during this period.) The mean age of the 5620 patients (18% female) was 55 years (range = 24-84 years), with approximately two-thirds between 50 and 69 years of age. A prior myocardial infarction was reported by 45%, and 74% reported chest pain. Of the patients with chest pain, its onset was reported within 1 year of the arteriography for 37%, 1-2 years before arteriography for 35%, and >2 years before arteriography for 29%.

Arteriograms were evaluated by a radiologist and cardiologist, without knowledge of risk-factor data. Reductions in lumen diameter (0%, 1-50%, 51-74%, 75-89%, 90-99% and 100%) in the left main, left anterior descending circumflex, and right coronary arteries were incorporated (summed) into an occlusion score indicating the overall severity of CAD. As previously reported [21, 25] a scale suggested by Rowe *et al.* [26] was modified, with a score of 0 representing no observed CAD, and a score of 300 denoting total occlusion of the major arteries. The number of diseased vessels (excluding the left main) was also calculated according to the number of ≥75% stenoses; this scale ranged from 0 to 3. (The correlation between the overall occlusion score and the number of diseased vessels was 0.90.) Disease in the left main vessel was considered clinically important if > 50% stenosis was observed.

Risk-factor information

Medical records and questionnaires we used to obtain data concerning obesity, alcohol consumption, smoking, and histories of hypertension, myocardial infarction, diabetes mellitus, and medication use for 3 months prior to catheterization. Persons were excluded from the current analyses if they reported use of oral contraceptives, sex hormones, thyroid or cholesterol-lowering medication, or had hypo- or hyperthyroidism. These restrictions eliminated 1074 patients, with persons using cholesterol-lowering drugs representing the largest number (n = 446) of exclusions. As compared with non-diabetics, a greater proportion of diabetics were eliminated by these exclusions. However, the difference was statistically significant only for hyperthyroidism: whereas 13% of the diabetics were hyperthyroid, the corresponding percentage among nondiabetics was 7% ($p = 0.02$).

Height and weight were used to calculate Quetelet Index (kg/m^2). Persons were considered to be hypertensive if they reported using antihypertensive medication. (Analyses performed using the patients' response to a question concerning past history of hypertension yielded similar results.) Usual alcohol intake, including beer, wine and mixed drinks, was converted to ounces of absolute alcohol per week. A 5-point smoking scale, reflecting both frequency and duration of smoking (1: never smoked, 5: smoked two or more packs daily for ≥20 years) was calculated as previously described [21]. (Even after controlling for both age and the number of daily cigarettes, smoking duration was related to CAD severity: partial correlations between duration (years) and occlusion score were 0.18 (males) and 0.23 (females) among current smokers, $p < 0.01$ for each association.) Smoking and alcohol data were available for 87% of the study population.

Following an overnight fast, blood samples were collected before arteriography. Plasma levels of total cholesterol and triglycerides were measured using automated procedures [27-29] in a standardized laboratory that is monitored by the Centers for Disease Control. Beginning in 1977, levels of HDL cholesterol were measured using procedures employed by the Lipid Research Clinics [29]; these measurements were available for 22% (*n* = 1230) of the patients in the current study. The ratio of total to HDL cholesterol was used as an estimate of the atherogenicity of each person's lipoprotein profile [30].

Definition of diabetes mellitus

Diabetic status was determined by using responses to three items on a questionnaire administered before catheterization:

1. Has your doctor ever said that you had diabetes?

2. Are you now taking or have taken diabetes pills or insulin shots within the past 3 months?

3. Have you been on a diet within the last year for diabetes?

Patients who responded "no" to all three questions *(n = 5154)* were considered to be non-diabetic. Persons were classified as diabetic if they had been told by a physician that they were diabetic and were using either

a. diet alone (*n* = 161),

b. medication alone (n = 42), or

c. both medication and diet (*n* = 234)

for control. In addition, 29 patients who reported using antidiabetic medication, but responded "no" to question 1 were also classified as diabetic. Unfortunately, fasting glucose levels were not available to confirm the identification of the diabetic patients.

Overall, there were 466 diabetics in the current analyses. Information concerning (1) the medication (insulin vs oral hypoglycemics) used for control, and (2) the duration and severity of diabetes was not obtained. However, the proportion of diabetics taking medication who used only oral hypoglycemics ranged from 70% [23] to 90% [24] in other arteriography studies.

Statistical analyses

The prevalence of diabetes was calculated for each sex according to 10-year age intervals, and levels of CAD and various risk factors were compared between diabetics and nondiabetics using 1-tests and chi-square tests. Analysis of covariance was also performed to control for small differences in age, yielding virtually identical results.

The relation of various risk factors to coronary artery occlusion was examined in non-diabetics and diabetics using Spearman correlation coefficients. Regression analyses were performed to determine whether the relation of diabetes to CAD existed independently of other risk factors, and standardized regression coefficients, calculated as $\beta(SD_x/SD_y)$, are used to compare the importance of each predictor variable. (Age and age^2 were expressed as deviations from the mean age (55.5 years) to reduce multicollinearity [31].) Possible effect modifiers were examined in both stratified and regression [32] analyses. A backwards elimination procedure was used to delete nonsignificant ($p > 0.05$) diabetes x risk factor interaction terms while controlling for the main effects. Two-tailed p-values are used in all analyses.

RESULTS

As background material, Fig. 1 shows the sex- and age-specific prevalence of diabetes among patients undergoing coronary arteriography. Overall, 8% of both males (381/4585) and females (85/1035) were classified as diabetic. In addition, the prevalence of diabetes increased with age, reaching 10.4% among 60-69-yearolds. Approximately three-fourths of the diabetics *(n = 362)* were between 50 and 69 years of age.

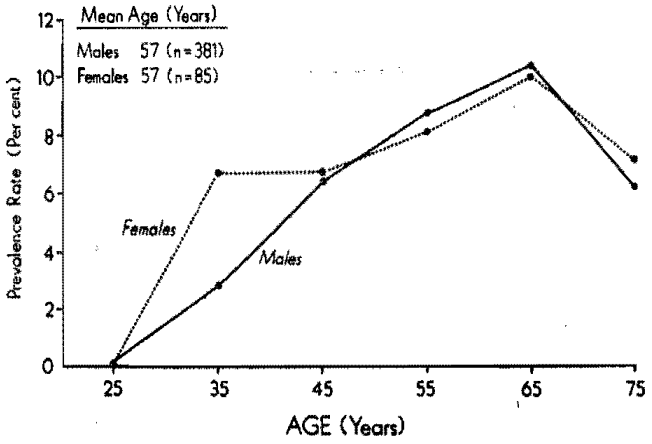

Fig. 1. Prevalence of diabetes mellitus in patients undergoing arteriography. The overall prevalence, according to a self-administered questionnaire, was 8% in both males and females. Approximately three-fourths of the diabetics were between the ages of 50 and 69 years.

Table 1 shows mean levels of selected characteristics according to diabetic status. Although the prevalence of chest pain was only slightly elevated among diabetics, larger differences were seen for both hypertension and previous myocardial infarction. As compared with non-diabetics, diabetics also had more extensive CAD and adverse levels of several risk factors, with most differences being proportionately larger among females. For example, mean occlusion scores increased by 24% (132-164) in male vs 60% (73-117) in female diabetics.

Table 1. Mean levels of selected characteristics, by sex and diabetes

	Males		Females	
	Nondiabetics ($n = 4204$)	Diabetics ($n = 381$)	Nondiabetics ($n = 950$)	Diabetics ($n = 85$)
Age (yr)	$55 \pm 9^{*,b}$	57 ± 8^{b}	56 ± 10	57 ± 9
Hx chest pain (%)	73	77	76	81
Hx hypertension (%)	38^{b}	47^{b}	48	59
Anti-hypertensive medication (%)	24^{b}	32^{b}	33^{a}	47^{a}
Hx myocardial infarction (%)	47^{a}	55^{a}	30^{a}	46^{a}
Treatment:				
Diet only (%)	—	36	—	28
Medication only (%)	—	13	—	14
Diet and medication (%)	—	51	—	58
Occlusion score	132 ± 86^{b}	164 ± 78^{b}	73 ± 86^{b}	117 ± 90^{b}
Number of diseased vessels	1.2 ± 1^{b}	1.5 ± 1^{b}	0.6 ± 1^{b}	1.0 ± 1^{b}
Left main disease (%)	6	7	2	4
Quetelet Index (kg/m^2)	26.6 ± 3.5	26.9 ± 3.5	25.9 ± 5.0^{b}	28.5 ± 5.1^{b}
Plasma total cholesterol (mg/dl)	234 ± 50^{a}	225 ± 50^{a}	236 ± 52	230 ± 44
Plasma triglycerides (mg/dl)	189 ± 125	203 ± 159	152 ± 89	200 ± 120
HDL cholesterol (mg/dl)†	38 ± 11^{a}	36 ± 9^{a}	47 ± 14	38 ± 13
Total/HDL cholesterol (mg/dl)†	6.0 ± 1.8	6.2 ± 1.8	5.2 ± 1.8	6.1 ± 1.5
Alcohol intake (oz/wk)	5.7 ± 7.1^{b}	3.4 ± 4.4^{b}	2.1 ± 3.1^{b}	0.9 ± 2.3^{b}
Smoking history	3.4 ± 1.4	3.4 ± 1.4	2.2 ± 1.4	2.4 ± 1.4
Current smokers (%)	18	15	18	17
Past smokers (%)	63	63	35	39
Never smokers (%)	19	22	47	44

*Mean ± SD.
†Restricted to patients with measured values for HDL cholesterol: 869 male nondiabetics, 104 male diabetics, 235 female nondiabetics, and 22 female diabetics.
t-Tests or chi-square tests were used to compare values between nondiabetics and diabetics.
[a] $p < 0.01$; [b] $p < 0.001$.

Additional analyses (data not shown) indicated that diabetics had increased CAD irrespective of the presence or duration (< 1, 1-2, or >2 years) of chest pain. Diabetes was not associated with increased levels of total cholesterol, but mean triglyceride levels were 24 and 48 mg/dl higher among male and female diabetics, respectively. Diabetics also showed decreased levels of HDL cholesterol (-2 mg/dl in males, -8 mg/dl in females), along with corresponding increases in total/HDL cholesterol. Differences in Quetelet Index were also seen: diabetes was associated with an average increase in weight of 5.3 kg (females) and 0.6 kg (males).

Table 2. Number of diseased vessels in diabetic patients

	Myocardial infarction							
	No				Yes			
	Males		Females		Males		Females	
Number of vessels ≥75% stenosed	Nondiabetics ($p = 0.001$)*	Diabetics	Nondiabetics ($p = 0.004$)	Diabetics	Nondiabetics ($p = 0.001$)	Diabetics	Nondiabetics ($p = 0.17$)	Diabetics
0	949 (43)†	49 (28)	483 (73)	23 (50)	345 (18)	26 (13)	112 (39)	9 (23)
1	609 (27)	52 (30)	98 (15)	10 (22)	716 (36)	58 (28)	93 (32)	15 (39)
2	454 (21)	40 (23)	53 (8)	9 (20)	569 (29)	69 (33)	50 (17)	11 (28)
3	203 (9)	32 (19)	27 (4)	4 (9)	350 (18)	55 (26)	34 (12)	4 (11)
Total	2215	173	661	46	1989	208	289	39

*Chi-square tests were used to compare the distribution of diseased vessels between nondiabetics and diabetics.
†Values represent frequencies (percent of myocardial infarction, sex, and diabetes category with specified number of stenosed coronary arteries).

The increased severity of CAD among diabetics was most pronounced in patients who had not suffered a previous myocardial infarction (Table 2). Among these patients, the prevalence of 3-vessel disease was approximately doubled among diabetics, both in males (9 vs 19%) and females (4 vs 9%). A proportionately smaller increase in 3-vessel disease (18 to 26%) was seen in diabetic males who had experienced a myocardial infarction. However, diabetes was only weakly associated with increased CAD among males who reported a myocardial infarction p = 0.17).

Regression analyses indicated that none of the risk factors showed a significantly stronger association with CAD among diabetics than among nondiabetics. Table 3 shows the relation of selected risk factors to coronary artery occlusion after stratifying by sex, previous myocardial infarction and diabetes. Among males, most associations were stronger in patients without a previous myocardial infarction, and among these patients, nondiabetics tended to show a stronger association between occlusion and levels of both total cholesterol and triglycerides than did diabetics. Among females, in contrast, associations between lipids and CAD tended to be stronger (but not significantly so) in diabetics than in nondiabetics, Using partial correlations to control for the effects of age yielded virtually identical results.

Table 3. Relation of occlusion score to selected risk factors; by sex, prior myocardial infarction, and diabetes

				Spearman correlation between occlusion score and:							
Sex	Prior MI status	Diabetes	(N)	Age	Total cholesterol	Triglycerides	HDL cholesterol*	Total/HDL cholesterol*	Quetelet Index	Alcohol intake	Smoking history
Males	$\overline{MI}$	No	(2047)	0.14[b]	0.22[b]	0.18[b]	−0.21[b]	0.29[b]	0	−0.06[a]	0.08[b]
		Yes	(173)	0.06[b]	0.12	0.06	−0.20	0.21	−0.08	−0.02	−0.02
	MI	No	(1989)	0.12	0.05	0.07[a]	−0.03	0.05	−0.03	−0.11[b]	0.04
		Yes	(208)	0.15	0.06	0.07	−0.05	0.03	0.01	−0.01	0.02
Female	$\overline{MI}$	No	(661)	0.28[b]	0.35[b]	0.28[b]	−0.23[b]	0.39[b]	0.03	−0.03	0.11[a]
		Yes	(46)	0.02	0.50[b]	0.51[b]	0.20	0.06	0.15	0.06	0.32
	MI	No	(289)	0.11	0.22[b]	0.22[b]	−0.21	0.26	0.09	−0.07	0.11
		Yes	(39)	0.39	0.39	0.43[a]	—†	—†	0.04	−0.28	−0.12

Abbreviation: MI, myocardial infarction; $\overline{MI}$, without myocardial infarction.
*Analyses are restricted to persons with HDL cholesterol measurements: 869 male nondiabetics, 104 male diabetics, 235 female nondiabetics, and 22 female diabetics.
†$N = 6$; correlation not shown.
[a]$p < 0.01$; [b]$p < 0.001$.

Regression analyses, including a sex x diabetes interaction term, indicated that diabetes was associated (p = 0.06) with a greater increase in occlusion among females than males. Analyses were then performed to assess whether the relation of diabetes to CAD was mediated through other risk factors, and Table 4 shows the results for each sex. Even after accounting for the effects of covariates, diabetes remained associated with an increased occlusion score in both males (+28) and females (+41). (The association between diabetes and CAD was particularly evident among patients who had not experienced a myocardial infarction.) Overall, diabetes and other risk factors accounted for more of the variability in CAD among females than among males: R^2 = 0.23 vs 0.08. Although most risk factors were significantly related to CAD in both sexes, antihypertensive medication was associated with CAD only in females.

Table 4. Regression of occlusion score on selected risk factors*

Independent variable	β		95% Confidence interval		Standardized β	
	Males	Females	Males	Females	Males	Females
Diabetes	28[b]	41[b]	(18, 37)	(22, 59)	0.09	0.13
Total cholesterol	0.23[b]	0.40[b]	(0.18, 0.29)	(0.29, 0.51)	0.14	0.23
Triglycerides	0.03[a]	0.10[a]	(0.01, 0.05)	(0.04, 0.16)	0.05	0.11
Quetelet Index	−0.56	−0.89	(−1.3, 0.19)	(−1.9, 0.14)	−0.02	−0.05
Antihypertensive medication	3.4	26[b]	(−2.6, 9.4)	(15, 37)	0.02	0.15
Alcohol intake	−1.2[b]	−1.5	(−1.6, −0.82)	(−3.2, 0.19)	−0.10	−0.05
Smoking history	5.5[b]	11[b]	(3.6, 5.8)	(6.9, 14)	0.09	0.17
Age	1.1[b]	1.8[b]	(0.84, 1.4)	(1.3, 2.3)	0.12	0.21
Age^2	−0.07[b]	0.01	(−0.09, −0.05)	(−0.03, 0.05)	−0.09	0.02
R^2 (full model)	0.08	0.23				

*Analyses are restricted to 3908 males and 862 females with recorded values for all variables.
[a]$p < 0.01$; [b]$p < 0.001$.

Including HDL cholesterol as a covariate in these analyses reduced the sample size to 1118 persons, but diabetes remained related to increased occlusion (+29, p = 0.0002). A 1 mg/dl increase in HDL cholesterol was associated with a -1.8 decrease in the occlusion score.

To examine whether other risk factors modified the relation of diabetes to CAD, stratified analyses were then performed. Within each risk-factor category, the mean occlusion score in nondiabetics, along with the increase among diabetics are shown in Table 5. For example, the 1083 male nondiabetics with cholesterol levels ≤200 mg/dl had a mean occlusion score of 112, whereas male diabetics with comparable cholesterol levels had a mean score of 154, an increase of 42.

The increased CAD among diabetics was similar across all age groups, and there was no evidence that the effect of diabetes in males was strongest at adverse levels of other risk factors. In contrast, at moderate to high levels of total cholesterol and triglycerides, female diabetics tended to show larger increases in CAD than did female diabetics with low levels of these lipids. In addition, whereas female diabetics who were using diet alone for control did not show increased coronary artery occlusion, those who used medication had a mean score of 133 (Table 5, bottom right). Regression analysis (Table 6) indicated that even after covariate adjustment, use of anti-diabetic medication in females remained associated with an increased (+66) occlusion score. (Similar increases in CAD were associated with medication irrespective of a previous myocardial infarction.) A comparable interaction between diabetes and antidiabetic medication was not observed among males. Although the sample size was greatly reduced if HDL cholesterol was included as a predictor variable, additional analyses indicated the relation of antidiabetic medication to CAD in females could not be attributed to levels of this lipoprotein cholesterol fraction.

Table 6 also shows the multivariable relation of risk factors to CAD according to diabetic status and sex. Irrespective of diabetic status, CAD was more strongly related to levels of total cholesterol than to triglycerides, and anti-hypertensive medication was associated with increased CAD only in females. In addition, the effects of alcohol intake (negatively), smoking history, and age were similar in both diabetics and nondiabetics.

Table 5. Mean occlusion scores according to selected risk factors and diabetic status

Risk factor	Males		Females	
	Nondiabetics Mean ± SD (*n*)	Diabetics Difference* (*n*)	Nondiabetics Mean ± SD (*n*)	Diabetics Difference* (*n*)
Age (yr)				
<50	113 ± 86 (1097)	26 (67)	50 ± 77 (232)	44 (16)
50–59	137 ± 85 (1755)	31 (167)	65 ± 81 (365)	47 (32)
⩾60	138 ± 85 (1352)	33 (147)	96 ± 89 (353)	36 (37)
Quetelet Index (kg/m^2)				
⩽25	132 ± 87 (1326)	32 (123)	67 ± 82 (466)	30 (22)
25–30	130 ± 84 (2151)	38 (178)	86 ± 89 (307)	54 (35)
>30	131 ± 86 (528)	16 (60)	67 ± 87 (153)	41 (27)
Plasma total cholesterol (mg/dl)				
⩽200	112 ± 87 (1083)	42 (125)	37 ± 64 (249)	27 (22)
201–250	132 ± 85 (1730)	41 (149)	72 ± 85 (366)	53 (40)
>250	145 ± 82 (1391)	17 (107)	100 ± 90 (335)	54 (23)
Plasma triglycerides (mg/dl)				
⩽150	119 ± 88 (1887)	35 (158)	55 ± 76 (582)	9 (33)
151–200	139 ± 85 (982)	29 (90)	91 ± 90 (182)	61 (21)
>200	143 ± 80 (1335)	30 (133)	112 ± 92 (186)	39 (31)
Total/HDL cholesterol				
⩽5.0	98 ± 86 (248)	49 (22)	50 ± 65 (119)	29 (7)
5.1–6.5	124 ± 78 (312)	45 (49)	93 ± 80 (69)	25 (7)
>6.5	150 ± 72 (309)	15 (33)	129 ± 88 (47)	3 (8)
Smoking status				
never	122 ± 89 (787)	41 (81)	61 ± 82 (438)	38 (36)
past	137 ± 83 (2590)	27 (236)	86 ± 86 (330)	63 (32)
current	124 ± 87 (749)	42 (56)	80 ± 89 (169)	7 (14)
Anti-hypertensive medication				
No	130 ± 87 (3194)	37 (260)	61 ± 78 (640)	42 (45)
Yes	137 ± 82 (1010)	20 (121)	98 ± 94 (310)	36 (40)
Anti-diabetic medication				
No	131 ± 86 (4204)	33 (137)	73 ± 85 (950)	4 (24)
Yes	—	33† (244)	—	60† (61)

*Difference: mean occlusion score in diabetics − mean occlusion score in nondiabetics.
†Increase in occlusion as compared with nondiabetics not using antihypertensive medication.

Table 6. Regression of occlusion score on selected risk factors*

Independent variable	Multivariable regression coefficient			
	Diabetics		Nondiabetics	
	Males	Females	Males	Females
Anti-diabetic medication	5.9 (0.04)†	66 (0.34)[b]	—	—
Total cholesterol	0.11 (0.07)	0.75 (0.35)[b]	0.25 (0.14)[c]	0.39 (0.24)[c]
Triglycerides	−0.01 (−0.02)	0.10 (0.14)	0.04 (0.06)[c]	0.09 (0.09)[a]
Quetelet Index	−0.85 (−0.04)	0.04 (0)	−0.55 (−0.02)	−0.97 (−0.06)
Antihypertensive medication	−0.20 (−0.12)[a]	23 (0.13)	5.8 (0.03)	27.4 (0.15)[c]
Alcohol intake	−0.25 (−0.02)	−1.7 (−0.04)	−1.3 (−0.11)[c]	−1.4 (−0.05)
Smoking history	3.1 (0.06)	14 (0.24)[a]	5.7 (0.09)[c]	10 (0.17)[c]
Age	1.6 (0.16)[b]	2.3 (0.23)[a]	1.1 (0.12)[c]	1.8 (0.21)[c]
Age^2	−0.11 (−0.11)	0.09 (0.12)	−0.07 (−0.09)[c]	0.01 (0.02)
R^2 (full model)	0.05	0.40	0.07	0.20

*Analyses are restricted to persons with recorded levels for all variables: 3592 male nondiabetics, 787 female nondiabetics, 316 male diabetics, and 75 female diabetics.
†Values are regression coefficient (standardized regression coefficient).
[a] $p \leq 0.05$; [b] $p < 0.01$; [c] $p < 0.001$.

DISCUSSION

Results of this study indicate that among patients undergoing arteriography, diabetes is independently related to increased coronary atheroschlerosis, and that its impact is proportionately greater in females than in males. Although adverse levels of several risk factors were observed among diabetic patients, their increased CAD cannot be attributed to levels of plasma lipids, HDL cholesterol, obesity, hypertension, cigarette smoking, or alcohol intake. However, associations between lipids and coronary artery occlusion tended to be slightly stronger in diabetic (vs nondiabetic) females. In contrast, among males who had not suffered a myocardial infarction, the relation of triglyceride levels to CAD was weaker among diabetics.

In agreement with current findings, several prospective studies [5-11] have shown that diabetics, especially female diabetics, are at increased risk for CHD even after adjustment for other risk factors. However, despite small numbers of CHD deaths among diabetics in many studies, it has been suggested that the risk of CHD may be particularly high among diabetics who smoke [16], are hypertensive [15], obese [17], hypertriglyceridemic [18], or who have low levels of HDL cholesterol [6]. In contrast, current results indicate that the effects of diabetes and other risk factors are mostly additive. The Whitehead [8] and Tecumseh [10] studies reported that CHD mortality among diabetics did not differ according to levels of total cholesterol, Quetelet Index, systolic blood pressure, or smoking status.

Although arteriography allows for the assessment of coronary atherosclerosis, rather than its clinical manifestations, several limitations of this study design [33] should be considered Because of its cross-sectional nature, it is necessary to assume that risk factors measured at time of arteriography accurately reflect levels in the past. In addition, patients undergoing arteriography are highly selected, and are not representative of all persons with CAD: cases of sudden death and massive myocardial infarction would be missed. Furthermore, because of possible referral biases among diabetics, the current results may overestimate the prevalence (and severity) of CAD among diabetics. For example, although 31% of the diabetics identified in a community-based (Rochester, Minn.) study had macrovascular complications, the corresponding percentage among hospitalized diabetics was 47% [34, 35]. In addition, because of autonomic neuropathy resulting in the reduction of chest pain [36], it is possible that only those diabetics with severe CAD would have been referred for arteriography. Although the prevalence of diabetes in the current study etas similar to that reported in a representative sample of the U.S. population [37], because of possible biases associated with hospital-based studies of CAD and diabetes, the current results should be extrapolated with caution.

In contrast, several other possible biases may have resulted in an underestimation of the association between diabetes and CAD. Obese female diabetics may suffer more lethal coronary events than do other diabetics [17], and if other risk factors also increase mortality among diabetics, associations may have been underestimated in the present study. Although controversial, diabetics may also have more diffuse CAD than do nondiabetics [19], and this could possibly reduce differences seen in arteriograms between a narrowed segment and a nearby "normal" arterial segment. In addition, the use of questionnaire data to assess diabetes likely resulted in false positives and false negatives. As suggested by Pearson [33], a diagnostic suspicion bias may have resulted in diabetics with less severe CAD symptoms undergoing arteriography.

Nevertheless, similarities with findings population-based studies argue against the possibility of a marked bias in the current results. The independent relation of diabetes (and other risk factors) to CAD, as well as its differential impact between males and females are in agreement with results obtained in prospective studies. Differences in levels of risk factors between nondiabetic and diabetic persons in the current study also parallel population-based findings. Although diabetics do not necessarily have increased levels of total cholesterol [6. 10, 11], diabetes (particularly in females) has been consistently related to obesity, elevated levels of blood pressure and plasma triglycerides [6, 7, 10, 11, 38], and to decreased levels of HDL cholesterol [38].

An unexpected finding was that the extent of coronary artery occlusion was particularly increased among females who were using anti-diabetic medications, even after adjustment for other risk factors. Hyperinsulinemia is often present in obese, type 2 diabetics or because of insulin therapy [39], and some

evidence suggests that insulin may be causally related to atherosclerosis [40]. However, although diabetics who use oral hypoglycemics [3, 41, 42] or insulin [4, 43[have been reported to be at increased risk for CHD, patients presenting with vascular disease have a high prevalence of carbohydrate abnormalities [44] and type 2 diabetes [45]. Unfortunately, information concerning specific medication use (or duration of diabetes) was not collected in the current study, but other arteriography studies [19, 20, 23, 24] found that approximately three-fourths of diabetics on medication were using oral hypoglycemics. Further studies are needed to determine whether antidiabetic medications are causally related to coronary atherosclerosis or reflect more severe diabetes of longer duration [18].

Results of this study indicate that diabetes is related to coronary atherosclerosis independently of other risk factors, and that its effect is relatively greater in females than in males. Although the independent contribution of diabetes atherosclerosis is not understood, abnormal protein composition, altered thrombogenic mechanisms or other genetic components [46] may be involved. However, the risk of clinical disease among diabetics, particularly among female diabetics, could be reduced by control of blood lipids, Obesity, smoking, and blood Pressure.

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